Exhibit B

Pharmacokinetics

SECOND EDITION, REVISED AND EXPANDED

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Determination of C_{max} and t_{max}

Mathematical relationships can be developed to estimate the time at which a peak plasma concentration of drug should be observed and the maximum plasma concentration at this time following first-order input into the body. Expanding Eq. (1.94) yields

$$C = \frac{k_a F X_0}{V(k_a - K)} e^{-Kt} - \frac{k_a F X_0}{V(k_a - K)} e^{-k_a t} \tag{1.102}$$

which when differentiated with respect to time gives

$$\frac{dC}{dt} = \frac{k_a^2 F X_0}{V(k_a - K)} e^{-k_a t} - \frac{k_a K F X_0}{V(k_a - K)} e^{-Kt} \tag{1.103}$$

When the plasma concentration reaches a maximum (C_{max}) at time t_{max}, $dC/dt = 0$. Therefore,

$$\frac{k_a^2 F X_0}{V(k_a - K)} e^{-k_a t_{max}} = \frac{k_a K F X_0}{V(k_a - K)} e^{-Kt_{max}} \tag{1.104}$$

which reduces to

$$\frac{k_a}{K} = \frac{e^{-Kt_{max}}}{e^{-k_a t_{max}}} \tag{1.105}$$

Taking the logarithm of both sides of Eq. (1.105) and solving for t_{max} yields

$$t_{max} = \frac{2.303}{k_a - K} \log \frac{k_a}{K} \tag{1.106}$$

For a given drug, as the absorption rate constant increases, the time required for the maximum plasma concentration to be reached decreases.

The maximum plasma concentration is described by substituting t_{max} for t in Eq. (1.94):

$$C_{max} = \frac{k_a F X_0}{V(k_a - K)} (e^{-Kt_{max}} - e^{-k_a t_{max}}) \tag{1.107}$$

However, a simpler expression can be obtained. From (1.105) it can be shown that

$$e^{-k_a t_{max}} = \frac{K}{k_a} e^{-Kt_{max}} \tag{1.108}$$

Substituting for $e^{-k_a t_{max}}$, according to (1.108), in (1.107) yields

$$C_{max} = \frac{k_a F X_0}{V(k_a - K)} \frac{k_a - K}{k_a} e^{-Kt_{max}} \tag{1.109}$$

which is readily simplified to

$$C_{max} = \frac{FX_0}{V} e^{-Kt_{max}} \tag{1.110}$$

The values of C_{max} and t_{max} under the special circumstance when $k_a = K$ is of mathematical interest and will be considered briefly. Under these conditions, Eq. (1.92) can be written as

$$\overline{X} = \frac{KFX_0}{(s + K)^2} \tag{1.111}$$

Hence

$$X = KFX_0 te^{-Kt} \tag{1.112}$$

$$C = \frac{KFX_0 te^{-Kt}}{V} \tag{1.113}$$

and

$$\log C = \log \frac{KFX_0 t}{V} - \frac{Kt}{2.303} \tag{1.114}$$

Equation (1.114) indicates that when $k_a = K$, a semilogarithmic plot of C versus t will contain no linear segments.

Differentiating Eq. (1.113) with respect to time yields

$$\frac{dC}{dt} = \frac{KFX_0}{V} e^{-Kt} - \frac{K^2 FX_0}{V} te^{-Kt} \tag{1.115}$$

At t_{max}, $C = C_{max}$ and $dC/dt = 0$. Therefore,

$$\frac{KFX_0}{V} e^{-Kt_{max}} = \frac{K^2 FX_0}{V} t_{max} e^{-Kt_{max}} \tag{1.116}$$